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MAR 1 4 2002
PATENT & TRADEMARK OFFICE

DECLARATION OF DR. JEFF NORDSTROM

Assistant Commissioner for Patents
Washington D.C. 20231

Sir:

1. I, Jeff Nordstrom, have worked extensively in the field of gene therapy, in particular, the regulation of transcription by steroid hormone receptors. My Curriculum Vitae is attached as Exhibit A.

2. I have reviewed the patent application entitled, "Mutated Steroid Hormone Receptors, Methods for Their Use and Molecular Switch For Gene Therapy," serial number 08/454,418, and the Office Action mailed March 30, 1998.

3. Experiments have been performed under my supervision that demonstrate the successful delivery using various routes of administration, in particular injection in the muscle, instillation to the lung, and delivery to the skin via a gene gun. Based on the results of these experiments and my knowledge regarding the general abilities and skill of those involved in this field, I would expect that other methods of delivery routes of administration would also be successful.

4. The intramuscular injection experiments measured the activity of a reporter gene (termed SEAP) *in vivo*. Expression was monitored in serum after 2 and 7 days and each time point was one day following administration of mifepristone at a dose of 25/mg/kg. The animals used were 50 eight-week old male Balb/C mice (20-25 grams) from Harlan Sprague Dawley. The animals were given anesthesia and injected inramuscularly into the right and left tibialis muscle with plasmids formulated in 5% PVP. Following delivery of formulated plasmids, groups of animals received vehicle (100µl sesame oil, ip), mifepristone (in 100 µl sesame oil, ip). Muscle tissue (each tibialis) or serum was harvested at defined time points. The results are shown in the graphs attached hereto as **Exhibits B and C**. The CMV-GS2.0 is a GeneSwitch construct of the claims with a C-terminal VP-16 domain. The CMV-GS3.1 is a GeneSwitch construct of the claims with a C-terminal p65 transactivation domain from human NFκβ. The results demonstrate that GeneSwitches of the claims can deliver and express a reporter gene *in vivo* when administered by intramuscular injection.

5. The instillation to the lung experiments also utilized the CMV-GS2.0 and CMVGS3.1 GeneSwitches. As shown in **Exhibit D** attached hereto, 5µg of DNA was instilled in the mouse lung , 50 µl formulated in DOTMA:Chol at a 1:3 -/+ complex charge ratio in 10% lactose. Groups D and F were dosed with 100 µl SesameOil on Day 0 and 1. Groups E and G were dosed with 100 ul Sesame Oil w/ 6.25mg/ml Mifepristone on Day 0 and 1. The results show successful delivery and expression of the SEAP reporter gene *in vivo* via lung instillation.

6. The gene gun delivery to the skin experiments were performed with Balb/c mice whose ears were shot with gold-DNA. The RU486 (500 mg/kg) was given ip to the mice 1 hour after shooting, and the luciferase activity of each ear was measured 24 hrs. later. The results showing in **Exhibits E and F** attached hereto show successful delivery and expression of a luciferase reporter gene following *in vivo* gene gun delivery to the skin.

7. As noted above, based on the results of these experiments and my knowledge regarding the general abilities and skill of those involved in this field, I would expect that other methods of delivery and routes of administration would also be

successful.

I declare that all statements made herein are of my own personal knowledge, are true and that all statements made on information and belief are believed true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Dated: 4-27-98

Jeff Nordstrom

OIPE
MAR 1 4 2002
PATENT & TRADEMARK OFFICE

Curriculum Vitae

Name: Jeffrey L. Nordstrom, Ph.D.

Address: GENEMEDICINE INC.
8301 New Trails Drive
The Woodlands, TX 77381-4248

Phones: (281) 364-1150
(281) 364-0858 (fax)

Education:

B.A. in Chemistry (A.C.S. approved); Colby College, Waterville, Maine; 1971.

Ph.D. in Biochemistry; Purdue University, West Lafayette, Indiana; 1976.
Thesis title: "Reversible Modulation of Rat Liver Hydroxymethylglutaryl Coenzyme A Reductase"

Employment Experience:

1976-77	Postdoctoral Fellow; Department of Biochemistry, Purdue University, W. Lafayette, Indiana; with Dr. Victor Rodwell.
1977-80	Postdoctoral Fellow; Department of Cell Biology, Baylor College of Medicine, Houston, Texas; with Dr. Bert O'Malley.
1980-87	Assistant Professor; Department of Biochemistry and Biophysics and Faculty of Genetics, Texas A&M University, College Station, Texas.
1987-94	Associate Professor; Department of Biological Sciences, Fordham University, Bronx, NY.
1994-95	Senior Scientist, Innovir Laboratories, Inc., New York, NY.
1995-96	Senior Scientist, GENEMEDICINE, INC., The Woodlands, TX
1996-97	Director, Gene Expression Systems, GENEMEDICINE, INC., The Woodlands, TX
1997-present	Director, Technology Discovery and Head, GeneSwitch Program, GENEMEDICINE, INC., The Woodlands, TX

Professional Societies:

American Association for the Advancement of Science (AAAS)
American Society of Biochemists and Molecular Biologists (ASBMB)
Sigma Xi

Professional Activities:

Teaching:

Texas A&M:	Undergraduate	MolecularGenetics
	Undergraduate	Biochemistry Laboratory
	Graduate	MolecularGenetics
	Graduate	Biochemistry
Fordham:	Undergraduate	Cell/Molecular Biology
	Undergraduate	Biochemistry
	Graduate	Biochemistry II
	Graduate	MolecularBiology
	Graduate	Seminar in Cell Biology (Oncogenes)
	Graduate	Seminar in Cell Biology (Steroid Hormones)
	Graduate	Genetic Analysis

Ph.D. Students:

Marco Kessler Ph.D., Texas A&M University, 1987.
Characterization of Sequences Involved in Polyadenylation of Eukaryotic Pre-mRNA.

Mark Westhafer Ph.D.,Texas A&M University, 1988.
Analysis of the SV40 Polyadenylation Signal.

Jingshan Chen Ph.D., Fordham University, 1993.
The Functional Components of the Mouse Beta-Globin Poly(A) Signal.

Patncia Dowling Ph.D., Fordham University, 1993.
Discovery of an Element in the Terminal Exon of the Mouse β-Globin Gene that Influences the accumulation of Spliced RNA.

Colette Saccomanno Ph.D., Fordham University, 1993.
Accumulation of Mouse Beta-Globin Transcripts in Transfected COS Cells is Influenced by the Identity and Arrangement of Pre-mRNA Processing Signals.

Michael Bordonaro Ph.D., Fordham University, 1995.
Processing of Genes with Intron or Splice Site Deletions.

Undergraduate Student Mentor:

Johanna Rivera, NIH Minority Access to Research Careers (MARC) program;1989- 1991.

High School Student Mentor:

Maxine Ashby (Roosevelt High School, Bronx NY), NIH Minority High School Student Research Apprentice Program; Summer 1988.

Mayumi Yamada (Bronx High School of Science, Bronx, NY), Completion of an independent biology research projectentitled, "Isolation, Amplification and Analysis of DNA from Ancient Equid Bones"; 9115/89 - 11/15/90.

Academic Program Review:

New Jersey Department of Higher Education consultant reviewer of the Program Approval Document for an Undergraduate Program in Molecular Biology at Montclair State College, Upper Montclair, NJ; January, 1990.

Sigma Xi, Fordham Chapter:
Vice President, 1989-90
President, 1990-91

Grants:
American Heart Association - Texas Affiliate: "Cloning of the Gene for HMG-CoA Reductase";7/1/81-6/30/84; $75,000.

NIH - National Heart, Lung and Blood Institute: "Regulation of the Gene for HMG-CoA Reductase"; 1/1/82-12/21/84; $103,476.

The Robert A. Welch Foundation: "The Enzymatic Mechanism of RNA Splicings; 6/11/82-5/31/85; $60,000.

Agricultural Biotechnology Expanded Research Area - Texas Agricultural Experiment Station: "RNA Processing and the Expression of Animal and Plant Genesn, 1/1/83-8/31/85, $80,000.

NIH Biomedical Research Support Grant: "Processing of Globin RNA Transcripts in Mouse Erythroleukemia Cells"; 4/1/83-3/31/84, $5,600.

NIH - National Institute of General Medical Sciences: "Signals for Polyadenylation of Globin and Other RNAs"; 4/1/84-3/31/87; $159,096.

The Robert A. Welch Foundation: Renewal of - The Enzymatic Mechanism of RNA Splicing"; 6/1/85-5/31/88; $60,000.

Agricultural Biotechnology Expanded Research Area - Texas Agricultural Experiment Station: Renewal of "RNA Processing and the Expression of Animal and Plant Genes", 9/1/85-8/31/87, $70,000.

NIH - National Institute of General Medical Sciences: Competitive renewal of "Signals for Polyadenylation of Globin and Other RNAs"; 4/1/87-3/31/82; $464,699.

Faculty Research Grant - Fordham University: "Molecular Archeology of Lemurs: Amplification and Analysis of DNA from Extant and Extinct Species"; 4/1/90-3/31/91; $4,000.

Faculty Research Grant - Fordham University: "DNA from Archeological Bone"; 4/1/92- 3/31/93; $3,800.

Publications:

Shapiro, D. M., Nordstrom, J. L., Mitschelen, J. J., Rodwell, V. W. and Schimke, R. T. (1974). Micro assay for 3-hydroxy-3-methyl-glutaryl CoA reductase in rat liver and in L-cell fibroblast. Biochim. Biophys. Acta 370: 369-377.

Rodwell, V. W., Nordstrom, J. L. and Mitschelen, J. J. (1976). Regulation of HMG-CoA reductase. Advan. Lipid Res. 14: 1-74.

Nordstrom, J. L., Mitcheleson, J. J. and Rodwell, V. W. (1977). Interconversion of active and inactive forms of rat liver hydroxymethylglutaryl-CoA reductase. J. Biol. Chem. 252:8924-8934.

Roop, D. R., Nordstrom, J. L., Tsai, M.-J. and O'Malley, B. W. (1978). Transcription of structural and intervening sequences in the ovalbumin gene and identification of potential ovalbumin mRNA precursors. Cell 15: 671-685.

Swaneck, G. E., Nordstrom, J. L., Kreuzeler, F., Tsai, M.-J., and O'Malley, B. W. (1979). Effect of estrogen on gene expression in chicken oviduct: Evidence for transcriptional control of ovalbumin gene. Proc. Natl. Acad. Sci. USA 76: 1049-1053.

Nordstrom, J. L., Roop, D. R., Tsai, M.-J., and O'Malley, B. W. (1979). Identification of potential ovomucoid mRNA precursors in chick oviduct nuclei. Nature 278: 328-331.

Tsai, M.-J., Ting, A. C., Nordstrom, J. L. and O'Malley, B. W. (1980). Processing of high molecular weight ovalbumin and ovomucoid precursor RNAs to messenger RNA. Cell 22: 219-230.

Swaneck, G. E., Colbert, D. A., Tsai, M.-J., Dugaiczyk, A., Woo S. L. C., and O'Malley, B. W. (1979). The ovalbumin gene: Organization, structure, transcription and regulation. Recent Progress in Hormone Research 35: 1-46.

Tsai, M.-J., Ting, A. C., Nordstrom, J. L. and O'Malley, B. W. (1980). Processing of high molecular weight ovalbumin and ovomucoid precursor RNAs to messenger RNA. Cell 22: 219-230.

Ciejok, El. M., Nordstrom, J. L., Tsai, M.-J., and O'Malley, B. W. (1982). Ribonucleic acid precursors are associated with the nuclear matrix. Biochemistry 21: 4945-4952.

Nordstrom, J. L., Hall, S. L., and Kessler, M. M. (1985). Polyadenylation of sea urchin histone RNA sequences in transfected COS cells. Proc. Natl. Acad. Sci. USA 82: 1094-1098.

Kessler, M. M., Beckendorf, R. C., Westhafer, M. A. and Nordstrom, J. L. (1986). Requirement of A-A-U-A-A-A and adjacent upstream sequences for SV40 early polyadenylation. Nucl. Acids Res. 14: 4939-4952.

Nordstrom, J. L. and Westhafer, M. A. (1986). Splicing and polyadenylation at cryptic sites in RNA transcribed from pSV2-neo. Biochem. Biophys. Acta 867: 152-162.

Kessler, M. M., Westhafer, M. A., Carson, D. D. and Nordstrom, J. L. (1987). Polyadenylation at a cryptic site in the pBR322 portion of pSV2-neo: Prevention of its utilization by the SV40 late poly(A) signal. Nucl. Acids Res. 15: 631-642.

Chen, J. S. and Nordstrom, J. L. (1992). Bipartite structure of the downstream element of the mouse beta (major) globin poly(A) signal. Nucl. Acids Res. 20:, 2565-2572.

Saccomanno, C. F., Bordonaro, M., Chen, J. S. and Nordstrom, J. L. (1992). A faster ribonuclease protection assay. BioTechniques 13: 846-850.

Bordonaro, M., Saccomanno, C. F. and Nordstrom, J. L. (1993). An improved T1/A ribonuclease protection assay. BioTechniques 16: 428-430.

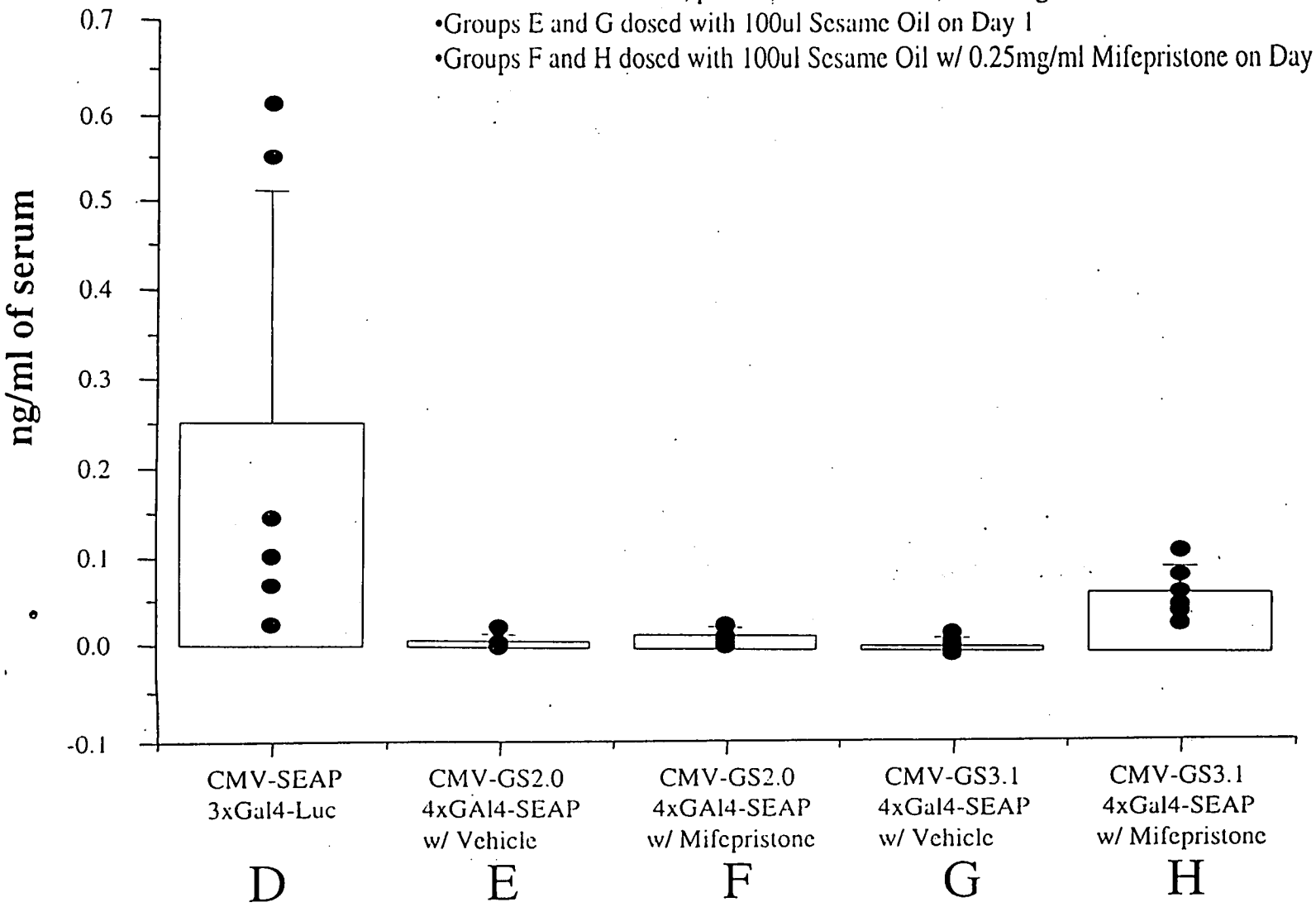
Bordonaro, M. and Nordstrom, J. L. (1994). Different mechanisms are responsible for the low accumulation of transcripts from intronless and 3' splice site deleted genes. Biochem. Biophys. Res. Commun. 203: 128-132.

Alila, H., Coleman, M., Nitta, H., French, M., Anwer, K., Liu, Q., Meyer, T., Wang, J., Mumper, R., Oubari, D., Long, S., Nordstrom, J. and Rolland, A. (1997). Expression of biologically active human insulin-like growth factor-I following intramuscular injection of a formulated plasmid in rats. Human Gene Ther. 8: 1785-1795.

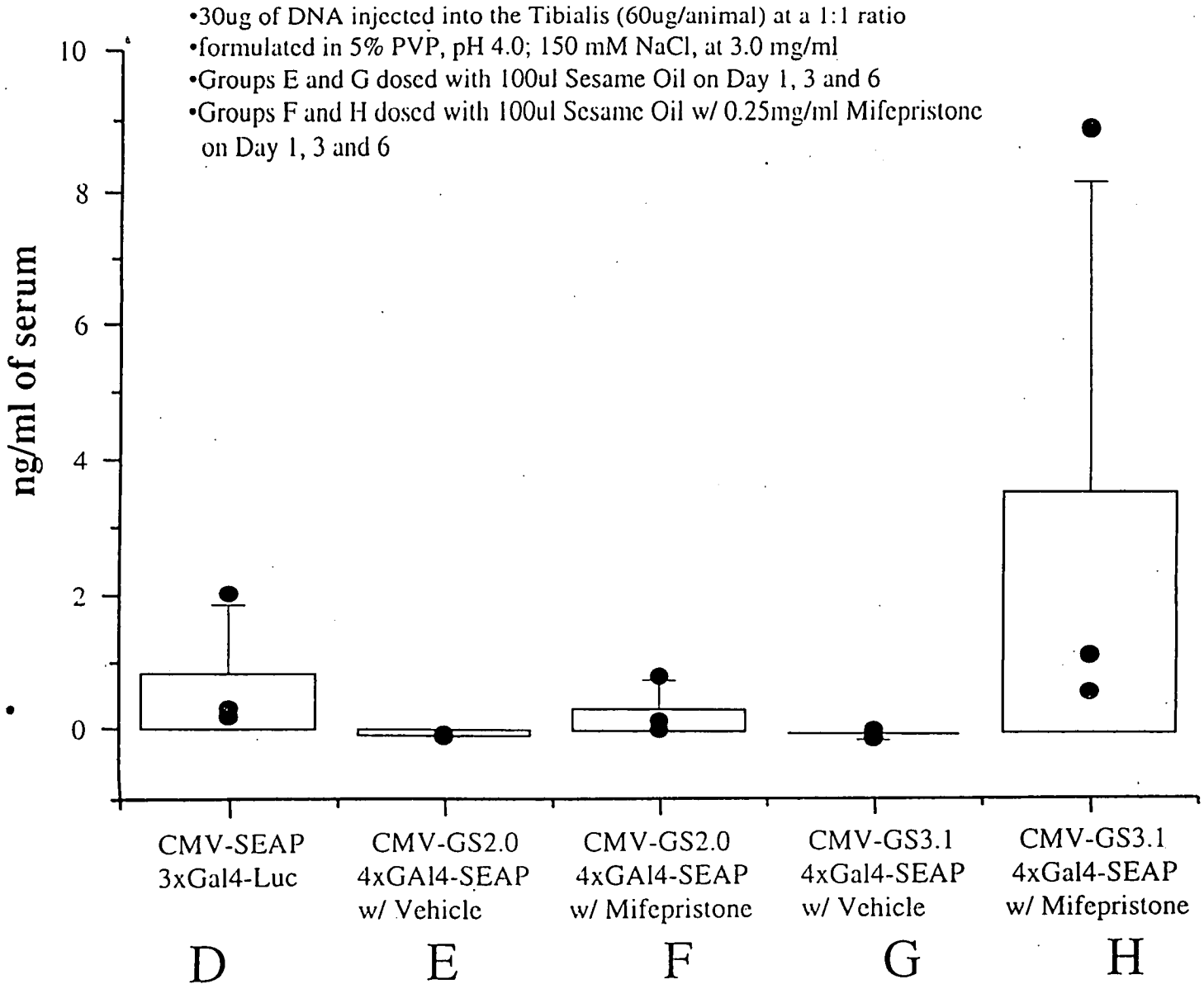
Freimark, B.D., Blezinger, H.P., Florack, V.J., Nordstrom, J.L., Long, S.D., Deshpande, D.S., Nochumson, S. and Petrak, K.L. (1998). Cationic lipids enhance cytokine and cell influx levels in the lung following administration of plasmid: Cationic lipid complexes. J. Immunol. 160: 4580–4586.

GS98007:
SEAP Activity at Day 2 After Injection Into Mouse Muscle

- 30ug of DNA injected into the Tibialis (60ug/animal) at a 1:1 ratio
- formulated in 5% PVP, pH 4.0; 150 mM NaCl, at 3.0 mg/ml
- Groups E and G dosed with 100ul Sesame Oil on Day 1
- Groups F and H dosed with 100ul Sesame Oil w/ 0.25mg/ml Mifepristone on Day 1

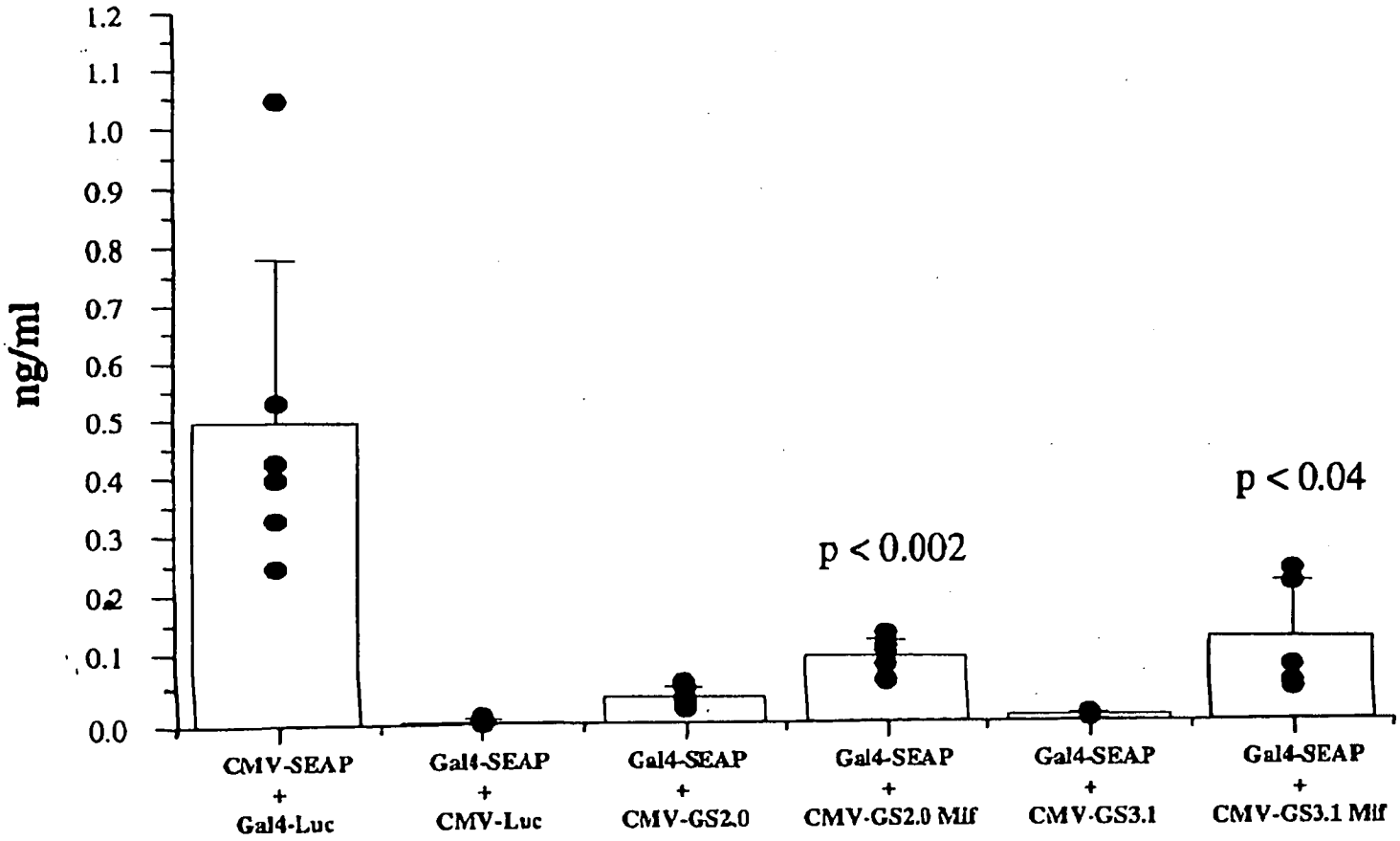


GS98007:
SEAP Activity at Day 7 After Injection Into Mouse Muscle



GeneSwitch™ Regulation of SEAP Expression *In Vivo*: Mifepristone-Dependent Secretion from Mouse Lung

- 5ug of DNA instilled in the mouse lung, 50ul
- formulated in DOTMA:Chol at a 1:3 -/+ complex charge ratio in 10% lactose
- Groups D and F dosed with 100ul SesameOil on Day 0 and 1
- Groups E and G dosed with 100ul Sesame Oil w/ 6.25mg/ml Mifepristone on Day 0 and 1



Gene Switch System in Luciferase Assay in Vivo

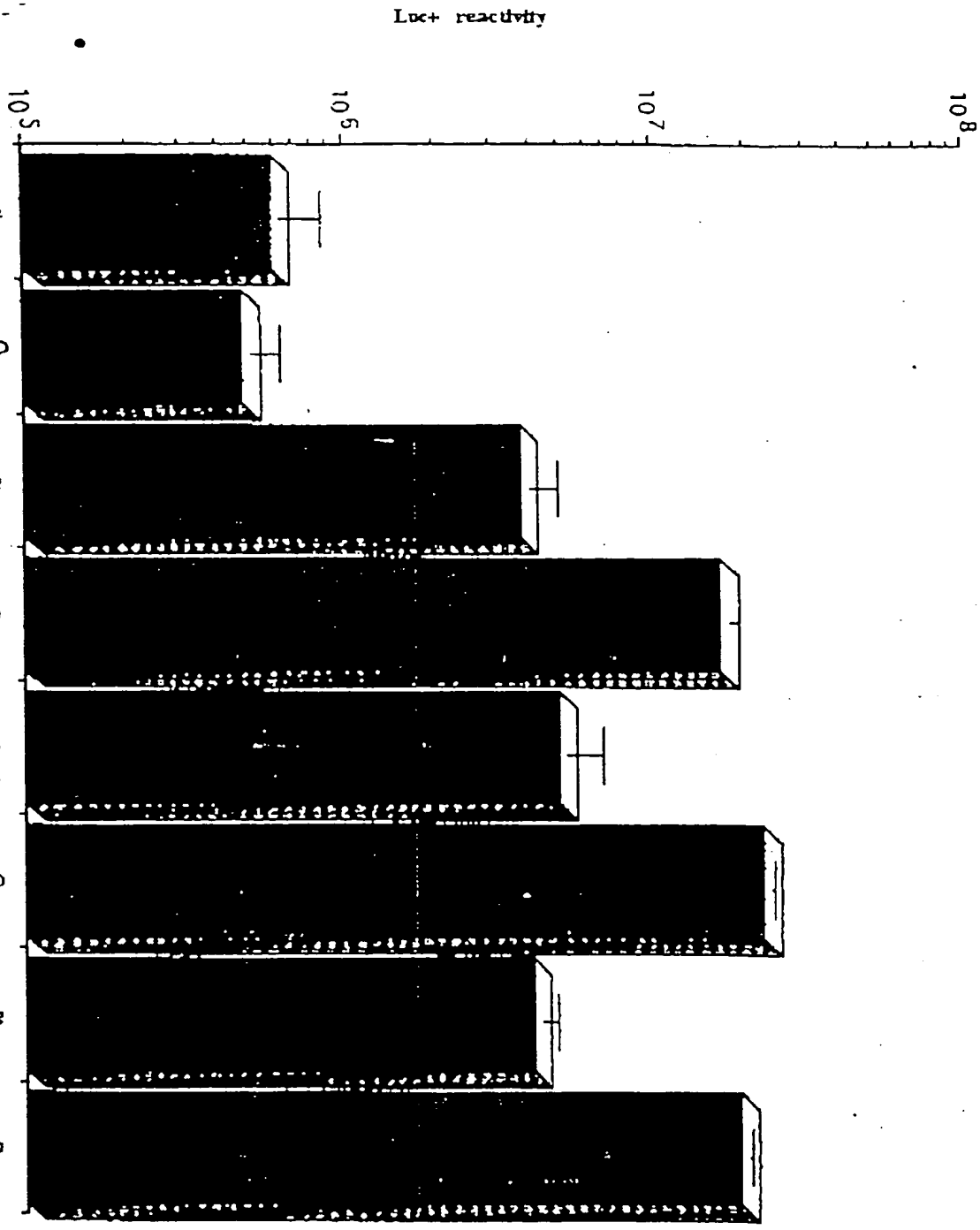
Protocols:

The mice (Balb/c) ears were shot with gold-DNA. The RU486 (500 mg/kg) was given ip to the mice 1 hr. after shooting, and the luciferase activity of each ear was measured 24 hrs later.

Luciferase activity

Vectors	DNA amouts of P4U-Luc +PGS0996	Luc activity per shot per ear (mean of two ears)	SE (two ears)	Fold of Induction
P4U-Luc	1 μg + 0	6.0×10^5	0.35	
P4U-Luc+Drug	1 μg +0	4.8×10^5	0.24	0.8
P4U-luc+PGS0996	1 μg + 10 ng	3.7×10^6	0.24	
P4U-luc+PGS0996+Drug	1 μg + 10 ng	1.7×10^7	0.07	4.5
P4U-luc+PGS0996	1 μg + 100 ng	4.9×10^6	0.30	
P4U-luc+PGS0996+Drug	1 μg + 100 ng	2.3×10^7	0.02	4.6
P4U-luc+PGS0996	1 μg + 1 μg	4.0×10^6	0.14	
P4U-luc+PGS0996+Drug	1 μg + 1 μg	1.9×10^7	0.01	4.8

1. P4U-luc also called PLC0998; 2. Drug used is RU486



P4U = w/ G4U binding sites
+D = w/drug